

# **Exhibit B**

United States Government Accountability Office

GAO

Report to Congressional Requesters

August 2008

# FOOD AND DRUG ADMINISTRATION

## Approval and Oversight of the Drug Mifeprex



G A O

Accountability \* Integrity \* Reliability

August 2008



Highlights of [GAO-08-751](#), a report to congressional requesters

## Why GAO Did This Study

In September 2000, the Food and Drug Administration (FDA), part of the Department of Health and Human Services (HHS), approved the drug Mifeprex for use in terminating early term pregnancy. FDA approved the drug under a provision of its Subpart H regulations, allowing it to restrict the drug's distribution to assure its safe use. Critics have questioned aspects of the Mifeprex approval process, including the reliance on historically-controlled clinical trials that compare a drug's effects on a condition to the known course of the condition rather than to another drug or placebo. Critics argued that Mifeprex does not fit within the scope of Subpart H, which applies to drugs that treat serious or life-threatening illnesses. Concerns have also been raised about FDA's oversight of the drug since approval, including the agency's response to deaths in U.S. women who had taken the drug.

In this report GAO (1) describes FDA's approval of Mifeprex, including the evidence considered and the restrictions placed on its distribution; (2) compares the Mifeprex approval process to the approval processes for other Subpart H restricted drugs; and (3) compares FDA's postmarket oversight of Mifeprex to its oversight of other Subpart H restricted drugs. GAO reviewed FDA regulations, policies, and records pertaining to its approval and oversight of Mifeprex and the eight other Subpart H restricted drugs. In addition, GAO interviewed FDA officials and external stakeholders.

To view the full product, including the scope and methodology, click on [GAO-08-751](#). For more information, contact Marcia Crosse at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov).

## FOOD AND DRUG ADMINISTRATION

### Approval and Oversight of the Drug Mifeprex

## What GAO Found

FDA approved Mifeprex after evaluating the sponsor's initial and revised new drug application through three review cycles. In the first cycle, FDA concluded that the available data supported the safety and efficacy of Mifeprex and that, because the course of pregnancy was well-documented and the effects of the drug were self-evident, the use of historical controls was consistent with FDA regulations. FDA also concluded that before the drug could be approved, the sponsor needed to provide final data from an ongoing U.S. trial, and more detail on restricting the drug's distribution. In the second cycle, FDA concluded that while the U.S. trial data confirmed the drug's safety and efficacy, the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In the final review, FDA concluded that termination of unwanted pregnancy is a serious condition and imposing restrictions under Subpart H was necessary. FDA approved Mifeprex, but required that the sponsor commit to conduct two postmarketing studies, imposed several distribution restrictions intended to ensure that only qualified physicians prescribe the drug, and required that patients attest to understanding the treatment's potential complications.

The approval process for Mifeprex was consistent with the processes for the other Subpart H restricted drugs, although the details of FDA's approval depended on the unique risks and benefits of each drug. Common elements of the approval processes included that FDA needed to evaluate potential limitations in key clinical data (Mifeprex and six of the other drugs), did not approve the drugs in the first review cycle (Mifeprex and five others), and imposed similar types of distribution restrictions on Mifeprex and the other drugs, though the specific details of the restrictions varied across the drugs.

FDA's postmarket oversight of Mifeprex has been consistent with its oversight of other Subpart H restricted drugs. To oversee compliance with distribution restrictions, FDA has reviewed data from all sponsors and conducted inspections for Mifeprex and two other drugs. To oversee compliance with postmarketing study commitments, FDA has relied on required updates from sponsors and found unfulfilled commitments for most drugs, including Mifeprex. To oversee compliance with adverse event reporting requirements, FDA has evaluated data in sponsors' reports and, for Mifeprex and seven other drugs, has conducted inspections that revealed deficiencies for most of these drugs, including Mifeprex. Lastly, FDA has taken similar steps to oversee postmarket safety across the drugs, such as analyzing adverse events. For Mifeprex, FDA investigated the deaths of six U.S. women who developed a severe infection after taking the drug and concluded that the evidence did not establish a causal relationship between Mifeprex and the infections. Finally, FDA has taken similar actions to address emerging safety concerns across the drugs, such as changing labeling.

HHS reviewed a draft of this report and informed GAO that it did not have comments.

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## Abbreviations

AERS	Adverse Event Reporting System
CDC	Centers for Disease Control and Prevention
ENL	erythema nodosum leprosum
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
HIV/AIDS	human immunodeficiency virus / acquired immune deficiency syndrome
NDA	new drug application
REMS	risk evaluation and mitigation strategy
SGE	special government employee

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United States Government Accountability Office  
Washington, DC 20548

August 7, 2008

The Honorable Michael B. Enzi  
Ranking Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable Jim DeMint  
United States Senate

The Honorable Roscoe G. Bartlett  
House of Representatives

In September 2000, the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) granted marketing approval to the prescription drug Mifeprex (mifepristone) for the medical termination of early term pregnancy.<sup>1</sup> It remains the only drug approved in the United States for this purpose. FDA approved the drug under a provision of the agency's Subpart H regulations that allows FDA to restrict the distribution or use of a drug in order to assure its safe use.<sup>2</sup> Under this provision FDA can require, as it did for Mifeprex, that distribution be restricted to certain health care providers with specific training or experience. Since the drug's approval, more than 900,000 women are estimated to have taken Mifeprex in the United States.

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<sup>1</sup>Mifeprex is the trade name for the mifepristone product marketed in the United States. Mifepristone is the name of the underlying drug substance. Mifepristone is also sometimes called "RU-486," a reference to the name the drug had during laboratory testing.

<sup>2</sup>Subpart H of FDA's drug approval regulations—titled "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"—applies to drugs that are intended to treat serious or life-threatening illnesses and provide a meaningful therapeutic benefit to patients over existing treatments. The regulations contain two approval provisions. One provides a process through which FDA may restrict the distribution or use of a drug to assure its safe use. The other provides FDA with flexibilities that allow the agency to accelerate the approval process for certain drugs on the basis of clinical trial endpoints that are considered reasonably likely to predict clinical benefit. See 21 C.F.R. §§ 314.500-560 (2007).

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Before a drug can be marketed in the United States, the drug sponsor must submit a new drug application (NDA) to FDA containing data demonstrating the safety and efficacy of the drug.<sup>3</sup> FDA reviews the NDA to determine whether the drug's benefits outweigh its risks.<sup>4</sup> Once FDA completes its review, the agency issues an action letter in which it either approves the drug as safe and effective for its intended use (approval letter), informs the sponsor that the drug is likely to be approved once the deficiencies FDA has identified are resolved (approvable letter), or indicates that approval cannot be obtained without substantial additional information (not approvable letter).<sup>5</sup> If FDA issues an approvable or not approvable letter, a subsequent review cycle can begin once the sponsor has addressed the issues FDA identified. FDA may require, as a condition of approval, that a sponsor agree to restrict the drug's distribution under the agency's Subpart H regulations.<sup>6</sup>

Critics have raised concerns and questions regarding several aspects of FDA's approval process for Mifeprex. For example, questions have been raised about the reliance on data from historically controlled clinical trials—trials that compare a drug's effects on a condition within the study population to the known course of that same condition in patients or

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<sup>3</sup>A drug sponsor is the person or entity who assumes responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

<sup>4</sup>FDA also reviews supplemental NDAs, which sponsors submit to support proposed changes to a drug's label, a new dosage or strength of the drug, a new patient population or intended use, or changes to the way the drug is manufactured after a drug has an approved NDA.

<sup>5</sup>FDA issued a final rule on July 10, 2008, amending its drug approval regulations. The final rule, among other things, discontinues FDA's use of approvable letters and not approvable letters. Instead, in the event that FDA determines it will not approve an application in its current form, the agency will send applicants a "complete response letter" to indicate that the review cycle for an application is complete and to describe the specific deficiencies the agency identified in the application. The amended regulations are effective on August 11, 2008. See 73 Fed. Reg. 39588-89 (July 10, 2008).

<sup>6</sup>21 C.F.R. § 314.520 (2007). From 1992—the year that the regulations were promulgated—through February 2007, nine drugs, including Mifeprex, had either an NDA or supplemental NDA approved under this restricted distribution provision. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA may determine that a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks. The REMS provisions of FDAAA went into effect on March 25, 2008. As part of a REMS, FDA can require "elements to assure safe use," which include restrictions similar to those that can be required under Subpart H regulations. 21 U.S.C. § 355-1(a), (e), (f); Pub. L. No. 110-85, §§ 901, 909(a), 121 Stat. 823, 922, 926-38, 950.

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populations that were not part of the trial—to support the safety and efficacy of Mifeprex.<sup>7</sup> FDA regulations allow for the use of such historical controls when the course of the condition in question is well-documented within a comparable population and the effect of the drug is apparent. Questions have also been raised about whether Mifeprex fit within the scope of Subpart H regulations, which apply to drugs that are intended to treat a serious or life-threatening illness. Critics have argued that unwanted pregnancy should not be considered a serious or life-threatening illness. They have also questioned whether FDA’s use of Subpart H regulations was consistent with its use of the regulations to approve other drugs.

Additionally, concerns have been raised about FDA’s postmarket oversight of Mifeprex, including its efforts to ensure the sponsor’s compliance with conditions of approval as well as the actions the agency has taken in response to reported adverse events.<sup>8</sup> For approved drugs, FDA oversees sponsors’ compliance with applicable reporting requirements, distribution restrictions, and other conditions of approval.<sup>9</sup> FDA also monitors the drugs’ postmarket safety and efficacy. In the case of Mifeprex, six U.S. women have died from severe bacterial infection after taking the drug, raising questions about its safety. Some have questioned FDA’s conclusion—which it discussed at a May 2006 congressional hearing—that the available evidence had not established a causal relationship between Mifeprex and the infections.

You asked us to review FDA’s approval of Mifeprex and its oversight of the drug since approval. In this report we (1) examine FDA’s approach to approving Mifeprex, including the types of evidence considered and the

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<sup>7</sup>21 C.F.R. § 314.126(b)(2)(v) (2007). In contrast, clinical trials that use concurrent controls demonstrate the safety and efficacy of a drug by comparing its effects on patients in a treatment group to the effects of a different treatment—such as another drug or a placebo—on patients in a control group within the same study population.

<sup>8</sup>The term postmarket refers to activities occurring after a drug has been approved for marketing. FDA uses the term adverse drug event to refer to any untoward medical event associated with the use of a drug in humans.

<sup>9</sup>FDA regulations require sponsors of approved drugs to submit various postmarket safety reports. See 21 C.F.R. §§ 314.80, 314.81 (2007). Additionally, sponsors of approved drugs must report to FDA annually on the progress of any postmarket studies required by FDA or agreed to by the sponsor. 21 U.S.C. § 356b; 21 C.F.R. § 314.81(b)(2)(vii) (2007). FDA uses such postmarket studies to gather additional information about a drug’s safety, efficacy, or use once it is marketed.



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restrictions placed on its distribution and use; (2) compare the approval process for Mifeprex to the approval processes for other drugs approved under the restricted distribution provision of Subpart H; and (3) compare FDA's oversight of the use of Mifeprex since its approval to the agency's oversight of the other drugs approved under the restricted distribution provision of Subpart H.

To examine FDA's approval of Mifeprex, we reviewed relevant laws, regulations, policies, and guidance. We reviewed FDA records including an archive of documents pertaining to the approval of Mifeprex.<sup>10</sup> We also reviewed documentation from an FDA advisory committee meeting,<sup>11</sup> testimony statements and the related transcript, FDA responses to congressional requests, an August 2002 citizen's petition and responses from outside organizations, and other documentation pertaining to FDA's approval of Mifeprex. We interviewed FDA officials and external stakeholders who had access to technical information or had conducted analyses pertaining to Mifeprex that were not available through FDA. These included a representative of the sponsor of the Mifeprex application and its licensee,<sup>12</sup> the American College of Obstetricians and Gynecologists and the American Association of Pro Life Obstetricians and Gynecologists.

To compare the approval process for Mifeprex to those of other drugs, we reviewed FDA documentation pertaining to FDA's approval of the other eight drugs that the agency had approved under the restricted distribution

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<sup>10</sup>In response to a Freedom of Information Act request, FDA posted certain documents pertaining to its approval of Mifeprex on the agency's Web site (see <http://www.fda.gov/cder/archives/mifepristone/default.htm>). The documents, which total over 9,000 pages, include a range of sometimes redacted material such as handwritten notes or email communications, communications between the drug sponsor and FDA, meeting minutes, copies of international labeling, and study protocols.

<sup>11</sup>FDA may convene an advisory committee to obtain advice from scientific experts and representatives of the public regarding a drug. FDA requests advice from advisory committees on a variety of matters, including aspects of drug applications and postmarket safety concerns for drug products. The primary role of an advisory committee is to provide independent advice that will contribute to the quality of the agency's regulatory decision-making. Although the committees provide recommendations to the agency, final decisions are made by FDA.

<sup>12</sup>The Population Council, a non-profit organization involved in reproductive health and population issues, sponsored the Mifeprex application. During the NDA review process, the Population Council contracted with Danco Laboratories, L.L.C. to serve as its licensee with responsibility for commercial manufacturing and marketing of the drug. Following the drug's approval, the Population Council transferred ownership of the Mifeprex NDA to Danco.

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provision of Subpart H as of February 2007.<sup>13</sup> Specifically, we examined key documents related to FDA's internal review and approval processes as well as documentation from advisory committee meetings in order to identify commonalities and differences in FDA's process across the nine Subpart H restricted drugs, including Mifeprex. In our examination we focused on issues that had arisen during FDA's review of Mifeprex to determine whether similar issues had arisen in FDA's review of the other drugs, and how FDA had addressed those issues for the other drugs.

To compare FDA's oversight of the use of Mifeprex since approval to the agency's oversight of the other Subpart H restricted drugs, we reviewed relevant regulations and FDA guidance. We also examined FDA documentation on the agency's oversight of sponsors' compliance with distribution restrictions, postmarketing study commitments, and adverse event reporting requirements for the nine Subpart H restricted drugs. In addition, we reviewed FDA's process for evaluating and responding to postmarket data on adverse events for each drug. Lastly, we interviewed FDA officials and staff who are responsible for postmarket oversight of these drugs. We conducted our work from February 2007 through August 2008 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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## Results in Brief

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of its Subpart H regulations after examining the NDA through three review cycles. In its first review, FDA concluded that the available evidence supported the safety and efficacy of Mifeprex. This conclusion was based in part on FDA's determination that because the course of pregnancy was well-documented and the effects of the treatment were self-evident, the reliance on historical controls in three key clinical trials—two conducted in France and one ongoing in the United States—was appropriate and consistent with FDA regulations. FDA issued an approvable letter in September 1996 concluding that the sponsor needed

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<sup>13</sup>We initiated our work in February 2007. In June 2007, FDA approved one additional drug—Letairis—under the restricted distribution provision of Subpart H. This drug was not included in our review.

to provide additional information, such as the final data from the U.S. trial and a detailed plan to restrict the drug's distribution, before an approval decision could be made. The second review cycle began when the sponsor submitted a complete response to this letter. FDA issued a second approvable letter in February 2000 after concluding that the new data confirmed the safety and efficacy of Mifeprex for the U.S. market but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. In its final review, FDA deliberated about the distribution restrictions and conditions of use needed to assure the safe use of the drug. FDA concluded that termination of an unwanted pregnancy is a serious condition and that the drug can allow patients to avoid a surgical procedure and therefore Mifeprex fit within the scope of Subpart H. FDA further concluded that the drug could only be used safely if distribution was limited to qualified physicians. The sponsor argued that the drug did not treat a serious condition and that because they had voluntarily agreed to the restrictions FDA had requested, it was neither appropriate nor necessary to impose the restrictions under Subpart H. However, the sponsor eventually acquiesced to FDA's requirement that approval be under Subpart H. After FDA concluded that the sponsor had adequately revised its distribution plan and addressed the remaining issues identified in FDA's reviews, it approved the Mifeprex NDA under Subpart H with several restrictions. These included requiring that prescribing physicians attest to possessing specific skills, agree to fully discuss the treatment with patients, and agree to report certain adverse events to the sponsor; that the drug be distributed directly to physicians by an authorized distributor; and that patients attest to fully understanding the treatment and its potential complications. The drug was also approved subject to the sponsor's commitment to conduct two postmarket studies related to patient outcomes.

The approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs, but the details of FDA's approval process for each drug depended on the drug's unique risks and benefits. One common element across the approval processes for seven of the drugs, including Mifeprex, was that FDA needed to evaluate potential limitations—such as lack of concurrent controls or small sample sizes—in key clinical trials supporting the NDA. For some of these drugs other than Mifeprex, FDA concluded that there were weaknesses in the data submitted in the NDA that needed to be addressed. Another common element for six of the drugs, including Mifeprex, was that FDA issued at least one prior action letter before ultimately approving the drug for marketing under Subpart H. Additionally, the types of distribution restrictions that FDA imposed on Mifeprex were similar to

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those the agency imposed on the other drugs, though the details of the restrictions varied depending on the drug. Lastly, eight of the drugs, including Mifeprex, were approved with two or more postmarketing study commitments, each with one or more commitments related to adverse events or patient outcomes of interest.

FDA's postmarket oversight of Mifeprex has been consistent with the agency's postmarket oversight of the other Subpart H restricted drugs. To oversee the drug sponsors' compliance with distribution restrictions, FDA has relied on data submitted by sponsors for all of the drugs. For three of the drugs, one of them Mifeprex, FDA has also completed inspections of the sponsor or its distributors. To oversee compliance with postmarketing study commitments, FDA has relied on updates in required reports from sponsors. Most of the drugs, including Mifeprex, have at least one study commitment that remains unfulfilled. To oversee compliance with adverse event reporting requirements, FDA has relied on sponsors' reports for all of the drugs and has also conducted inspections of the sponsor or its manufacturers for eight of them. FDA has cited the sponsors of seven of the drugs, including Mifeprex, for adverse event reporting deficiencies. To oversee the postmarket safety of all of the Subpart H restricted drugs, FDA has routinely conducted reviews of adverse event reports to monitor for safety concerns. In the case of Mifeprex, FDA investigated the deaths of six U.S. women who developed a fatal infection following treatment with Mifeprex for medical abortion. FDA has determined that in all six of the deaths, the women used a Mifeprex treatment regimen that has not been approved by FDA. Based on its investigations, FDA has concluded that a causal relationship between the use of Mifeprex and the fatal infections has not been established. FDA has also monitored other kinds of adverse events and has concluded that, with the exception of the cases of fatal infection, reported serious adverse events associated with Mifeprex have been within or below the ranges it expected. Additionally, for Mifeprex and the other drugs, FDA has taken similar actions—such as issuing warnings and requesting changes to the product labeling—to communicate safety information to consumers and health care providers.

HHS reviewed a draft of this report and informed us that it did not have general comments. In addition, HHS provided technical comments which we incorporated as appropriate.

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## Background

The Mifeprex NDA provided for the use of Mifeprex, in combination with another drug, for the medical termination of pregnancy. The treatment regimen described in the NDA involved taking Mifeprex orally, and then taking the drug misoprostol orally 2 days later unless termination of the pregnancy had already occurred.<sup>14</sup> Patients return for a follow-up visit with their prescribing physician 2 weeks later to ensure that the termination of the pregnancy has been completed. The treatment regimen works by both interrupting the hormones that the body needs to maintain a pregnancy and inducing the uterine cramping necessary to cause a medical abortion.

At the time that the drug sponsor submitted the Mifeprex NDA, in March 1996, mifepristone had already been approved in multiple countries. The drug was first approved for the medical termination of pregnancy in France and China in 1988.<sup>15</sup> It was approved subsequently in the United Kingdom in 1991, in Sweden in 1992, and various other European countries throughout the 1990s. In general, the treatment regimens approved in these countries were similar to those studied in the Mifeprex NDA, though in some cases the specific drug used in combination with mifepristone was different.

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## FDA Application Review Process

FDA reviews drug applications to determine whether they provide sufficient evidence to demonstrate that a drug is safe and effective for the proposed use, including whether the benefits of the drug outweigh its risks. FDA's formal process for new drug approval begins after a drug sponsor submits an application, typically following a long period of research and development. During a preliminary review, FDA determines whether the application is sufficiently complete to be reviewed and if so, designates it for either standard or priority review, depending on the

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<sup>14</sup>Misoprostol is one of several drugs that had been studied in combination with mifepristone for the medical termination of pregnancy because they have been shown to induce uterine contractions. However, it is approved for marketing in the United States for a different indicated use.

<sup>15</sup>The company that discovered mifepristone and manufactured it for marketing in France—Roussel Uclaf—did not want to produce the drug for the U.S. market. Instead, the U.S. sponsor retained a contract manufacturer. For a more detailed discussion of the history of the development of mifepristone for the U.S. market, see: Congressional Research Service, *Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)*, (Washington, D.C.: 2001).

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therapeutic potential of the drug.<sup>16</sup> The agency then assigns a team of reviewers—including medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts—within the relevant FDA review division. This review team, which is usually led by a medical officer, conducts a comprehensive evaluation of the clinical and non-clinical information in the application including the safety and efficacy data for the drug, the design and quality of the studies used to support the application, and the proposed labeling for the drug and also reviews the results of inspections of the facilities where the drug is manufactured.<sup>17</sup> The review team compiles the results of its analyses and recommends either an approval, approvable, or not approvable action.

FDA managers, usually including the review team's supervisor and senior management within the applicable review division, determine what action to take on an application, based on the recommendations of the review team. These managers examine the review team's analysis and individually decide whether to concur with the recommendation. The final decision on the action the agency should take is usually, but not always, made by the director of the applicable review division. In some cases, actions must be reviewed and agreed to by the relevant FDA office.

This review process may span several cycles. For those applications not approved during the first review cycle—both approvable and not approvable—the second FDA review cycle begins once the sponsor submits an amendment to the application providing responses to the deficiencies FDA identified in its previous review. These amendments often contain additional studies, analyses, data, or clarifying information to address FDA's concerns. The responsible review team reviews the information provided by the sponsor, conducts any additional analyses that are required, reviews the results of any additional inspections that have been conducted, and again recommends either an approval, approvable, or not approvable action. As with the first review cycle, the process ends once FDA management reviews the recommendations of the

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<sup>16</sup>FDA may grant priority review status when it determines that a drug may provide significant benefits in the treatment, diagnosis, or prevention of a disease as compared to marketed drugs or non-drug therapies, such as surgery, or provide a treatment where no adequate therapy exists.

<sup>17</sup>The non-clinical data in an NDA pertains to, for example a drug's chemistry, manufacturing, and controls as well as its toxicology and pharmacology.

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review team and makes its decision on the action to take on the application.

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## Restricting Drug Distribution and Subpart H Regulations

To address concerns FDA identifies regarding the safe use of a drug, the agency may condition approval by requiring that the sponsor agree to restrict the drug's distribution. FDA has established restricted distribution programs for approved drugs primarily by requiring that a drug's approval be under the restricted distribution provision of Subpart H regulations. According to the scope of the regulations, Subpart H applies to new drugs that "have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments" for the condition.<sup>18</sup> FDA may approve a drug under the restricted distribution provision of these regulations if it meets these criteria and the agency concludes that the drug is effective but can be safely used only if distribution or use is restricted. For example, FDA may require that distribution of a drug be limited to certain facilities or physicians with special training.

As of February 2007, nine drugs—Actiq, Accutane, Lotronex, Mifeprex, Plenaxis, Revlimid, Thalomid, Tracleer, and Xyrem—had either an NDA or supplemental NDA approved under the restricted distribution provision of Subpart H.<sup>19</sup> For each of the drugs, either during the application review process or based on postmarket data, FDA identified concerns about the safe use of the drug that led the agency to apply Subpart H. The drugs were approved to treat a range of conditions, such as breakthrough cancer pain, specific symptoms of narcolepsy, and severe acne.

FDA has also required that drug sponsors agree to restrict the distribution of drugs without imposing Subpart H. Clozaril, Tikosyn, and Trovan are three examples of drugs that have restricted distribution programs that were imposed outside of Subpart H. (See app. I for a table describing drugs FDA has approved with restricted distribution programs and the conditions they are intended to treat). While Clozaril was first approved in

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<sup>18</sup>21 C.F.R. § 314.500 (2007).

<sup>19</sup>21 C.F.R. § 314.520 (2007). The sponsor for Plenaxis—approved in 2003 for the palliative care of certain patients with advanced prostate cancer—withdrew the product from the market in 2006. Additionally, three generic versions of Accutane have been approved for marketing under this restricted distribution provision.



1989, FDA imposed distribution restrictions on both Tikosyn and Trovan after Subpart H regulations had been promulgated.

A second approval provision of Subpart H provides FDA with flexibilities that allow the agency to accelerate the approval process for drugs that provide meaningful therapeutic benefits over alternatives for serious or life-threatening illnesses.<sup>20</sup> Specifically, under the provision, FDA may approve a drug on the basis of clinical trials establishing that the drug has an effect on a surrogate endpoint—such as weight gain or reduced occurrence of infections in patients with HIV—that is reasonably likely to predict a clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.<sup>21</sup> This allows FDA to approve a drug before measures of effectiveness that would usually be required for approval are available. However, under this approval provision, drug sponsors are ordinarily required to conduct postmarket studies to confirm and further describe the drug's clinical benefit. As of February 2007, FDA had used this provision to approve 52 drugs, most of which are intended to treat HIV/AIDS or various cancers.

## FDA's Role in Postmarket Oversight

Because some risks may not become known until after a drug's approval and use in a wider segment of the population, FDA has a range of postmarket oversight responsibilities once a drug is approved for marketing in the United States. FDA's postmarket oversight responsibilities include assessing sponsors' compliance with requirements for a given drug, such as postmarketing study commitments, adverse event reporting, and restricted distribution requirements. In addition, FDA monitors reported adverse events to assess the postmarket safety of approved drugs and may take action if it develops a concern about a drug's safety.

With regard to postmarketing study commitments, FDA oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report to FDA annually on their progress in meeting the

<sup>20</sup>See 21 C.F.R. § 314.510 (2007).

<sup>21</sup>According to FDA, although some surrogate endpoints are recognized as well-established and have long been a basis for approval (such as change in blood pressure or cholesterol), accelerated approval regulations allow reliance on a "surrogate endpoint that, while 'reasonably likely' to predict clinical benefit, is not so well-established as the surrogates ordinarily used as bases of approval in the past." 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).



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commitments. FDA requires that sponsors report on the status of these studies in an annual report that also includes updates on the distribution of the drug, labeling changes, clinical literature published on the drug, and the drug's marketing.<sup>22</sup> FDA designates unfulfilled study commitments as submitted, pending, ongoing, delayed, released, or terminated.

FDA also oversees sponsors' compliance with regulations that require sponsors of all approved drugs to report periodically to FDA on safety information and specific types of adverse events that occur in association with an approved drug.<sup>23</sup> Sponsors must provide in periodic reports (quarterly for the first 3 years after approval and annually thereafter) a narrative summary and analysis of adverse event information. For adverse events that are considered both serious and unexpected,<sup>24</sup> sponsors are required to submit a report—known as a “Postmarketing 15-day Alert Report”—to FDA within 15 calendar days from the time the sponsor was informed of the event. To assess sponsors' compliance with these adverse event reporting requirements, FDA reviews sponsors' reports and conducts inspections of the sponsors' reporting policies and procedures.

For drugs approved under the restricted distribution provision of Subpart H, FDA oversees sponsors' compliance with the restrictions placed on the drugs' distribution or use. To assess compliance with restrictions, FDA reviews information such as summaries of sponsors' distribution programs in annual reports and in some cases separate reports required by the agency to provide details and updates on distribution programs. In addition, FDA may conduct inspections of a sponsor's corporate headquarters, manufacturing sites, or contractors, such as specialty distributors, to evaluate whether distribution policies and procedures comply with the approved restrictions for a given drug. If FDA identifies deficiencies during an inspection, it may issue a formal citation—known as a Form FDA 483. In addition, FDA may communicate less serious findings as written or oral “observations” or “recommendations.”<sup>25</sup>

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<sup>22</sup>See 21 C.F.R. § 314.81 (2007).

<sup>23</sup>See 21 C.F.R. § 314.80 (2007).

<sup>24</sup>Unexpected events are those that are not included in the current labeling for a drug.

<sup>25</sup>FDA uses the same reporting scheme—noting citations, observations, or recommendations—for its inspections to assess sponsor compliance with adverse event reporting.

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To monitor postmarket safety of approved drugs, FDA reviews clinical literature, routinely evaluates the available data on reported adverse events, and conducts investigations of the nature and patterns of these events. FDA compiles data from sponsor's reports on adverse events, along with data from voluntary reports submitted to the MedWatch program, in its Adverse Event Reporting System (AERS) database.<sup>26</sup> FDA safety evaluators analyze data from AERS and in the clinical literature to detect signs of potential safety concerns. These evaluations may reveal the need for further studies of a drug or may result in FDA action to ensure the safety of the drug.<sup>27</sup>

If FDA identifies problems with a sponsor's compliance with agency requirements or identifies postmarket safety concerns, the agency can take a range of actions to address the concern and communicate safety information to healthcare providers and the public. For example, FDA may revise the restrictions on a drug's distribution, request changes to a drug's labeling, issue patient advisories or public health alerts, or request that a sponsor issue letters to health care providers or pharmacists to alert them to safety concerns. FDA may also issue a regulatory letter citing violations of laws or regulations. Typically, FDA issues a Warning letter for violations that may lead FDA to pursue further enforcement action if not corrected or issues an untitled letter for violations that do not meet this threshold. FDA also has the authority to withdraw a drug's marketing approval for safety-related and other reasons,<sup>28</sup> although it rarely does so. Additionally,

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<sup>26</sup> MedWatch is a voluntary reporting program through which health professionals and consumers can report adverse reactions, product problems, and use errors related to drugs and other products approved by FDA.

<sup>27</sup> GAO has previously reported on and made recommendations regarding FDA's postmarket oversight of approved drugs. See GAO, *Drug Safety: Improvements Needed in FDA's Postmarket Decision-making and Oversight Process*, [GAO-06-402](#). (Washington, D.C.: Mar. 31, 2006).

<sup>28</sup> 21 U.S.C. § 355(e).

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Subpart H regulations establish an expedited process for withdrawing a drug's marketing approval, in certain circumstances.<sup>29</sup>

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## FDA Approved Mifeprux under the Subpart H Restricted Distribution Provision After Concluding That Clinical Evidence Supported Its Safety and Efficacy

FDA approved Mifeprux after three review cycles. In its initial review, FDA concluded that reliance on historical controls in three key clinical trials was appropriate and consistent with FDA regulations and that the available data supported the safety and efficacy of the drug. In an approvable letter, FDA notified the sponsor that it needed to provide additional data and more detail on its proposal to restrict the drug's distribution before an approval decision could be made. A second review cycle began when the sponsor submitted data responding to this letter. The agency issued a second approvable letter after finding that new data confirmed Mifeprux's safety and efficacy but also that the sponsor needed to revise its distribution plan and address labeling and manufacturing deficiencies. FDA further concluded that the drug was a candidate for approval under Subpart H. In the final review cycle, FDA concluded that the sponsor's revised distribution plan and other revisions were sufficient to address FDA's comments. FDA also concluded that Mifeprux met the scope of Subpart H and that approval under the restricted distribution provision of Subpart H was necessary to ensure that only qualified physicians prescribed the drug. On September 28, 2000, FDA approved Mifeprux under the restricted distribution provision of Subpart H with several restrictions and two postmarketing study commitments. (See table 1 for a timeline of key events in the Mifeprux approval process.)

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<sup>29</sup>Under Subpart H regulations, FDA may withdraw a drug's marketing approval after providing for a hearing, in the following circumstances: (1) a postmarketing clinical study fails to verify clinical benefit; (2) the sponsor fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product; (4) the sponsor fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use. 21 C.F.R. § 314.530 (2007).

**Table 1: Timeline of Key Events in FDA's Approval of Mifeprux**

Date	Event
<b>First review cycle</b>	
March 1996	The sponsor submitted a new drug application (NDA) for the use of Mifeprux in combination with the drug misoprostol for the medical termination of intrauterine pregnancy.
July 1996	FDA Reproductive Health Drugs Advisory Committee meeting.
September 1996	FDA issued an approvable letter listing issues that the sponsor needed to address before the application could be approved.
<b>Second review cycle</b>	
August 1999	After delays securing a manufacturer, the sponsor completed its responses to FDA's 1996 approvable letter.
February 2000	FDA issued a second approvable letter, listing issues that the sponsor needed to address prior to approval.
<b>Third review cycle</b>	
March 2000	The sponsor completes its responses to FDA's second approvable letter.
September 2000	FDA approved Mifeprux under the restricted distribution provision of Subpart H.
November 2000	Distribution of Mifeprux began in the United States.

Source: GAO analysis of FDA and drug sponsor data.

### FDA's Initial Review Cycle and Approvable Action (March to September 1996)

FDA's initial review began when the drug sponsor submitted the Mifeprux NDA in March 1996. After conducting a preliminary review of the NDA, FDA designated the application for priority review, establishing a goal that the agency would issue an action letter within 6 months. FDA's rationale for the designation was that as the first drug that would be approved for its particular indication, Mifeprux was a therapeutic advance because women using the drug could potentially avoid the risks of surgery and anesthesia involved in a surgical termination of a pregnancy.

FDA assigned a team of reviewers within the Division of Reproductive and Urologic Drug Products to review the evidence in the Mifeprux NDA. The key safety and efficacy data in the NDA consisted of three historically controlled clinical trials, two conducted in France and one conducted in the United States. These trials studied the Mifeprux treatment regimen—mifepristone in combination with misoprostol—in a total of more than 4,000 women. At the time the NDA was submitted, the French trials were complete and the U.S. trial was ongoing. As a result, during the first review cycle, the review team analyzed the complete safety and efficacy data from the French clinical trials, but only summary data on serious adverse events

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from the U.S. clinical trial. FDA reviewers also considered results from other trials conducted in Europe from 1983 through 1996 in which mifepristone was studied either alone or in combination with misoprostol or similar drugs. In addition, the review team considered safety information from extensive postmarketing experience in Europe, including a postmarket safety database containing information on women who had used mifepristone. Lastly, the review team considered the non-clinical data in the application, including data on the drug's chemistry and manufacturing.

In its review of the Mifeprex data, FDA reviewers determined that the reliance on historical controls in the key clinical trials was appropriate and consistent with FDA regulation. According to FDA, historical control designs can make it more difficult to evaluate which effects can be attributed to the drug being studied.<sup>30</sup> However, FDA regulations list historical controls as an acceptable type of control when the natural history of the condition being treated is well-documented and when the effects of the drug are self-evident.<sup>31</sup> In the case of the Mifeprex NDA, FDA determined that the historically controlled trials provided substantial evidence of safety and efficacy because the outcomes of women taking the Mifeprex regimen were compared with the well-documented data on the natural course of pregnancy, including rates of miscarriage, and the effect of the drug—termination of a pregnancy—was obvious.<sup>32</sup>

To assist the review team in its assessment of Mifeprex, FDA convened the Reproductive Health Drugs Advisory Committee in July 1996 and asked the members to examine the data and vote on their conclusions regarding the drug's safety and efficacy. Six of the eight voting members voted, with

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<sup>30</sup>See FDA, *Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials* (Rockville, Md.: May 2001).

<sup>31</sup>21 C.F.R. § 314.126(b)(2)(v) (2007). The regulation also states that studies that are “adequate and well-controlled” provide the primary basis for determining whether there is “substantial evidence” in support of the claims of effectiveness for new drugs. Among other things, an adequate and well-controlled study provides sufficient details of study design, conduct, and analysis to allow critical evaluation, and the design must permit a valid comparison with a control to provide a quantitative assessment of the drug's effect.

<sup>32</sup>FDA has cited examples of other drugs that have relied upon historical controls. According to FDA, for contraceptives the effect of the drug can be compared to the well-documented rate of pregnancy in sexually active women between the ages of 15 and 35 in the absence of contraception. For example, FDA approved the contraceptive drug products Lybrel, Implanon, Yaz, and NuvaRing on the basis of historically controlled clinical trials.

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two abstentions, that the available evidence demonstrated that the benefits of the regimen outweighed its risks for the proposed indication in the United States. However, the members agreed unanimously that FDA should provide the final safety and efficacy data from the U.S. clinical trial for their review. The advisory committee also discussed the basic elements of a voluntary restricted distribution system proposed by the drug's sponsor, which would require that Mifeprex be distributed directly to physicians, that prescribing physicians meet certain training requirements, and that patients meet certain conditions before receiving the drug. The advisory committee voted unanimously that they agreed with the concept of restricting distribution of the drug but had reservations about how the proposed system would assure that physicians had adequate credentials. The members recommended that the sponsor conduct postmarket studies to address six unanswered questions about the treatment regimen and the distribution system. The members also provided extensive comments on the draft labeling proposed by the sponsor.

The FDA review team concluded that the NDA was approvable, based on its assessment of the clinical and non-clinical data and the input from the advisory committee. The medical officer leading the review team concluded that the available clinical data indicated “that medical abortion can be safely delivered in a wide variety of United States settings.” The data from the French trials showed the treatment to be roughly 95 percent effective at terminating pregnancy through 49 days gestation. The data from the French clinical trials also showed that almost all patients experienced some side effects—such as uterine cramping and bleeding—most of which were expected based on the way the drug works. Though serious adverse events were considered rare, some women experienced bleeding that required medical intervention, and approximately 0.2 percent of patients required transfusion. The medical officer concluded that the preliminary U.S. data on adverse events did not appear to differ significantly from the French trials.<sup>33</sup>

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<sup>33</sup>The medical officer noted that it was only possible to make general comparisons across these events because definitions and reporting requirements were different in the two countries. Additionally, while the sponsor had not yet completed its analysis of the safety and efficacy data from the U.S. clinical trial, information from the studies was forwarded to the sponsor weekly. The medical officer concluded, based on preliminary examination of this information, that the final results of the U.S. trials were likely to be similar to the results of the French trials.

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In September 1996, FDA issued an approvable letter for the use of Mifeprex in combination with the drug misoprostol for the termination of intrauterine pregnancy up to 49 days gestation. In memos documenting concurrence with the review team, and in the approvable letter itself, FDA management outlined the clinical and non-clinical issues the sponsor needed to address prior to approval. First, the full data from the U.S. clinical trial were needed to establish safety and efficacy of the Mifeprex regimen in the U.S. health care setting. Second, FDA agreed with the sponsor's proposal to limit the drug's distribution, but the sponsor had not yet submitted sufficient detail on how it would be implemented to allow for the plan to be fully evaluated.<sup>34</sup> Third, the drug labeling proposed by the sponsor needed to be revised to provide more information on the treatment and to address comments from the advisory committee. Fourth, the sponsor would need to commit to pursue the postmarket studies suggested by the advisory committee. Finally, the sponsor would need to address certain deficiencies in chemistry and manufacturing data identified in FDA's review.

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### FDA's Second Review Cycle and Approvable Action (August 1999 to February 2000)

FDA's second review cycle for the Mifeprex NDA officially began once the sponsor had completed its responses to the first approvable letter. However, these responses were delayed because of difficulties the sponsor encountered in securing a manufacturer for the drug product. In the interim, the sponsor submitted a range of data to FDA, including the final safety and efficacy results from the U.S. clinical trial, updated safety data from other trials of mifepristone and international postmarketing experience with the drug, formal revisions of the product labeling, and outstanding chemistry and manufacturing data. In August 1999, the sponsor completed its responses to the approvable letter by submitting an overview of the key principles of the restricted distribution system as well as responses to the postmarketing study commitments. At the time of this submission, the sponsor was still working with its planned distributor on the details of the restricted distribution system.

Based on the updated data, the review team recommended approval for the Mifeprex NDA once the sponsor had clarified the details of the drug's distribution, revised the drug labeling, and addressed deficiencies in the

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<sup>34</sup>FDA management's concurrence memos noted that because the sponsor had voluntarily proposed a restricted distribution system, imposing restrictions through Subpart H regulations did not appear warranted.



chemistry and manufacturing data. The medical officer concluded that the final results from the U.S. clinical trial were acceptable and confirmed the results of the French trials that the regimen was safe and effective.<sup>35</sup> The medical officer concluded that the comments from the July 1996 advisory committee meeting were fully considered and, to the extent possible, implemented.<sup>36</sup> The medical officer also concluded that additional detail was needed to determine whether the sponsor's proposed distribution plan was sufficient. The non-clinical reviews during this review cycle—which included inspections of manufacturing facilities<sup>37</sup>—identified deficiencies in the drug's chemistry data and manufacturing processes that needed to be addressed, as well as sections of the drug's labeling that needed to be revised.

In January 2000, the sponsor submitted a more detailed plan describing how the proposed distribution restrictions would be implemented. The plan had three key elements. First, the Mifeprex regimen would only be administered under the supervision of qualified physicians who had agreed to provide the treatment according to several guidelines. Specifically, prescribing physicians would be required to attest to being able to accurately assess the duration of a pregnancy, diagnose an ectopic pregnancy,<sup>38</sup> and assure that patients have access to appropriate follow up care if needed to manage complications. The physicians would also need to agree to fully explain the procedure to each patient and obtain her

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<sup>35</sup>The U.S. clinical trial data showed the treatment to be 92 percent effective for terminating pregnancy through 49 days gestation, which was slightly lower than the 95 percent from the French trials. Adverse event rates were also slightly higher in the U.S. trials. The medical officer attributed these differences to the relative inexperience of U.S. clinicians with the treatment. In addition, the medical officer concluded that the updated information from international studies, postmarket experience, and the published literature was consistent with the results from the U.S. and French trials.

<sup>36</sup>In November 1999, FDA provided advisory committee members the final results from the U.S. clinical trial for their review and comment. FDA did not receive any comments from the members on these results.

<sup>37</sup>The drug substance (mifepristone) in the Mifeprex product was manufactured by the Shanghai Haulian Pharmaceutical Co., Ltd., with the manufacturing facilities located in China. Initial FDA inspections found the manufacturer not in compliance with FDA's good manufacturing practice standards.

<sup>38</sup>Ectopic pregnancy—which occurs when a fertilized egg improperly implants outside of the uterus—is a contraindication for receiving the Mifeprex regimen. Accurate screening to ensure that patients with an ectopic pregnancy do not receive the treatment was a concern because a ruptured ectopic pregnancy is a life-threatening condition and its symptoms are similar to the side effects of the Mifeprex regimen.



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signed consent, record the unique product serial number for tracking purposes, and report any serious adverse event or on-going pregnancy to the sponsor. Second, the drug would only be distributed directly to physicians after an authorized distributor had verified that the physician had registered with it and had a signed attestation on file. Third, patients would be required to meet certain conditions before receiving the drug, such as signing a patient agreement attesting to her understanding of the potential complications of the treatment.

FDA management concluded that the proposed distribution plan did not provide for adequate training and certification of prescribing physicians and needed to be revised before the NDA could be approved. In February 2000, FDA issued a second approvable letter for Mifeprex, notifying the sponsor that it needed to revise its proposed distribution plan, address deficiencies in the drug's chemistry data and manufacturing, and revise the drug's labeling. The letter also stated that FDA had considered the application under the restricted distribution provision of Subpart H and that distribution restrictions would be necessary in order to assure the safe use of the drug. The approvable letter further reminded the sponsor of its commitment to pursue postmarketing study commitments to address questions that were raised at the time of the advisory committee meeting.

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### FDA's Final Review Cycle and Marketing Approval for Mifeprex (March to September 2000)

In March 2000, the sponsor submitted its complete response to FDA's February 2000 approvable letter. This submission included updated safety data from ongoing trials and international postmarket experience, international product labeling, and revisions to the distribution plan. The sponsor also provided additional data and revisions—including updated chemistry and manufacturing data, a revision to the distribution plan, and revised labeling—to address comments from FDA that arose during the review cycle. The agency's review of these submissions included multiple meetings and teleconferences with the sponsor and input from a consultant who was a special government employee (SGE) and a member of the Reproductive Health Drugs Advisory Committee.<sup>39</sup>

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<sup>39</sup> According to FDA, it is not uncommon for the agency to consult with members of its advisory committees who have special expertise in a particular drug under review. Generally, an SGE is defined as an officer or employee who is retained, designated, appointed, or employed by the government to perform temporary duties, with or without compensation, for not more than 130 days during any period of 365 consecutive days. 18 U.S.C. § 202(a).

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During the final review cycle, FDA's deliberations—which involved a wide range of agency staff and management, including at times the Commissioner—focused on four key issues: whether prescribing physicians should be required to participate in a formal training and certification program, whether to require that approval be under Subpart H, what conditions of use should be specified, and what postmarketing study commitments would be needed to assure the safe use of the drug.

- **Physician Training:** In its deliberations, FDA considered requiring that physicians participate in specific training and have their qualifications certified before being allowed to prescribe Mifeprex, as opposed to relying on the sponsor's proposed system of self-attestation. However, FDA concluded that such a requirement was not necessary. FDA officials told us that the agency determined that its concern about ensuring that prescribers were adequately qualified could be addressed by requiring that the sponsor make educational materials and training programs readily available and requiring that prescribing physicians sign an agreement attesting to their qualifications. The SGE consultant agreed with this conclusion. FDA officials also told us that the agency wanted to minimize the burden that the restricted distribution program would place on providers and patients by requiring only what was necessary to address safety concerns.<sup>40</sup>

In July 2000, the sponsor submitted its revised distribution plan. This plan addressed FDA's comments by providing increased emphasis in the product labeling on the educational materials and trainings available to physicians and the importance of participating in the training. The other key elements of the plan—including the specific qualifications that physicians were required to meet and agreements regarding discussing the treatment and adverse event reporting—were essentially unchanged from those the sponsor proposed in its January 2000 plan.

- **Approval under Subpart H Regulations:** FDA had maintained through the first two review cycles that distribution restrictions would be required for Mifeprex. However, minutes from meetings between FDA and the sponsor indicate that the agency was still considering whether it was necessary to impose those restrictions under Subpart H during the final review cycle. During the second review cycle, FDA had concluded that the restricted

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<sup>40</sup>Subpart H regulations state that any restrictions imposed will be commensurate with the specific safety concerns presented by the drug product. 21 C.F.R. § 314.520(b) (2007).

distribution provision could be applied to Mifeprex.<sup>41</sup> FDA eventually concluded that it would be necessary to do so. In its documented rationale for this conclusion, FDA stated that the drug met the scope of the regulations because the termination of an unwanted pregnancy is a serious condition, and that the drug provided a meaningful therapeutic benefit over existing therapies by allowing patients to avoid the procedure required with surgical termination of pregnancy. FDA officials told us that the agency has broad discretion to determine which conditions or illnesses may be considered serious or life threatening, and that in the case of Mifeprex it considered the potential in any pregnancy for serious or life-threatening complications—such as hemorrhage—in its determination.<sup>42</sup> Additionally, FDA concluded that Mifeprex could only be used safely if distribution was limited to physicians who could assess the duration of a pregnancy, diagnose an ectopic pregnancy, and provide patients with access to surgical intervention if necessary.

Throughout the approval process, the sponsor was opposed to approval under Subpart H. Specifically, the sponsor argued that the drug did not fit within the scope of Subpart H because pregnancy itself is not a serious or life threatening illness. The sponsor also argued that the intent of the restricted distribution provision was to allow for restricted distribution of highly toxic or risky drugs, and that Mifeprex did not fit this description.<sup>43</sup> The sponsor also expressed concern that approving the drug under Subpart H could unfairly mark Mifeprex as risky and deter women from using the drug. Lastly, the sponsor held that imposing Subpart H was unnecessary because it had voluntarily committed to the distribution

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<sup>41</sup>FDA had also noted that approving the drug under Subpart H would allow the agency to impose similar restrictions on any future generic mifepristone products approved for the same indication. The patent for Mifeprex expired in October 2004, but as of May 2008, no generic versions of mifepristone have been approved for marketing.

<sup>42</sup>The terms “serious” and “life-threatening” are not defined in Subpart H regulations, but were discussed in the preambles to the proposed and final rules. In its proposed rule, FDA stated that the seriousness of a disease is a matter of judgment, but generally is based on its impact on survival, day-to-day functioning, or other factors, and provided examples of conditions that could be within the scope of the regulation. FDA noted that many diseases or conditions can be serious for some populations in some or all of their phases and explicitly reserved the discretion to determine whether the regulations were applicable to a given product. See 57 Fed. Reg. 13234-5 (Apr. 15, 1992), 57 Fed. Reg. 58942, 58946 (Dec. 11, 1992); See also 21 C.F.R. §§ 312.34, 312.81 (2007), and FDA, *Guidance for Industry: Fast Track Drug Development Programs—Designation, Development, and Application Review* (Rockville, Md.: Jan. 2006).

<sup>43</sup>In support of its arguments about the intent of the regulations, the sponsor cited the pertinent language from preambles to the proposed and final rules. See footnote 42.

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restrictions requested by FDA. However, in a September 2000 letter to FDA, the sponsor agreed to FDA's requirement that approval be under Subpart H, while noting that it still believed that applying these regulations to Mifeprex was not appropriate.

- Conditions of Use: FDA reviewed data and held multiple meetings with the sponsor regarding the specific conditions of use that should be required for Mifeprex. For example, FDA deliberated about whether it was necessary to require that prescribing physicians possess the ability to perform follow-up surgical interventions in the event that it was necessary to manage complications. The sponsor maintained that such a requirement was inconsistent with the practice of medicine, because management of incomplete miscarriages was routinely handled by referring patients to outside providers with specialized surgical or emergency care training. On this issue, FDA concluded that access to follow-up care could be ensured by requiring adequate information in the labeling and requiring that physicians attest to having made arrangements for their patients to have access to any needed surgical or emergency care. The SGE consultant agreed with FDA's conclusion. FDA disagreed with the sponsor on other suggested conditions of use. For example, the sponsor provided data to support allowing patients to self-administer the misoprostol dose at home, instead of requiring them to return to their prescribing physicians. FDA concluded that the available data did not support the safety of home use of misoprostol and that such use should not be included in the final product label. As a part of its deliberations about the conditions of use, FDA also concluded that approved labeling should include a medication guide to provide patients with information about the risks and benefits of the drug and the approved conditions of use and treatment regimen.<sup>44</sup>
- Postmarketing Study Commitments: In both the September 1996 and February 2000 approvable letters, FDA had reminded the sponsor of its commitment to conduct a series of six postmarket studies to address comments raised in the 1996 advisory committee meeting. FDA reviewed data and met with the sponsor during the final stages of its review to revisit these commitments in light of experience gained with the treatment regimen since the advisory committee meeting, concerns about potential infringement on the privacy of patients, and the potential resources needed to fulfill all six commitments. FDA concluded that the originally proposed commitments could be sufficiently addressed in two redesigned

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<sup>44</sup>FDA may require that a drug be distributed with a medication guide that provides patients with information about the safe and effective use of the drug. See 21 C.F.R. pt. 208 (2007).

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studies. The first was a study on the safety outcomes of a group of patients receiving the treatment under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention when necessary. The second was a surveillance study to determine the outcomes of ongoing pregnancies that were not surgically terminated after a failure of the Mifeprex regimen, including the health of any children born. FDA also concluded that the outstanding questions could be incorporated into the two postmarket studies and an audit of signed patient agreement forms.

Once the sponsor had addressed the issues that FDA raised during the third review cycle, both the review team responsible for the Mifeprex NDA and FDA management concluded that the drug should be approved. The medical officer concluded that the updated safety data did not reveal any new issues that would change the ratio of benefit-to-risk for the drug. The medical officer also reviewed revised product labeling related to the distribution of the drug. Based on these reviews, the medical officer recommended approval of the application. The non-clinical reviews during this review cycle included additional inspections of manufacturing facilities. After the sponsor had addressed several issues, including deficiencies identified in a second inspection of the drug manufacturing facilities, the non-clinical reviewers also recommended approval of the application. FDA management concurred with the recommendations of the review team that the Mifeprex NDA should be approved.

On September 28, 2000, FDA approved Mifeprex under the restricted distribution provision of Subpart H. The sponsor began distribution of Mifeprex in November 2000. FDA approved the drug with the two postmarketing study commitments discussed above and with several key restrictions on distribution. First, prescribing physicians must sign a prescriber's agreement attesting to possessing the training and skills needed to administer the treatment regimen, and also agreeing to provide patients with the approved medication guide. They must also attest that they will fully discuss the treatment with patients and report to the sponsor any serious adverse events or ongoing pregnancies that are not terminated after a failure of the Mifeprex regimen. Second, the drug must be distributed directly to prescribing physicians by an authorized distributor only after the distributor has verified that the physician has a signed agreement on file. Third, patients must sign a patient agreement attesting to having read, discussed, and understood the risks and potential complications of the treatment. For a more detailed list of the individual components of the restricted distribution program for Mifeprex, see

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appendix II. For a copy of the approved prescriber's agreement, see appendix III.

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## Approval Process for Mifeprex Was Generally Consistent with That of the Other Eight Subpart H Restricted Drugs

Although each drug had unique risks and benefits, the approval process for Mifeprex was generally consistent with the approval processes for the other eight Subpart H restricted drugs. Each of the drugs had unique risks and benefits that were specific to their indication and target populations. For some of the drugs, the safety issues that prompted FDA to apply Subpart H were similar, with the potential for causing birth defects, the potential for liver or other serious toxicities, and appropriate patient selection being the most common issues. However, there were also safe use concerns that were unique to particular drugs. For example, for Mifeprex, ensuring patient access to follow-up care was a key safety concern, while for Actiq a key concern was ensuring that children did not accidentally ingest the drug.<sup>45</sup> Each of the drugs represented potential advances in the treatment of their targeted condition and in two cases—Mifeprex and Xyrem—the drug was the first approved to treat that condition. (See app. I for a table including each of the Subpart H restricted drugs and their approved indications.)

One common element across the approval processes for the Subpart H restricted drugs was that for seven of the drugs, including Mifeprex, FDA needed to evaluate potential limitations in key clinical data supporting the NDA. Specifically, with the exception of Accutane and Lotronex, the drugs were approved on the basis of studies without concurrent controls or data that were limited by relatively small sample sizes or data collection issues.<sup>46</sup> FDA approved the Mifeprex NDA on the basis of historically controlled clinical trials that studied the drug in several thousand patients. FDA concluded that the use of historical controls was not a limitation

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<sup>45</sup> Actiq contains the controlled substance fentanyl in a lozenge formulation intended to allow for more rapid delivery of the medication for pain management in patients who have developed a tolerance. Because of the formulation there are concerns that Actiq may be perceived by children as a lollipop.

<sup>46</sup> Both Accutane and Lotronex were approved under Subpart H after they had first been marketed in the United States. In the case of Lotronex, the sponsor withdrew the drug from the market in 2000 because of safety concerns. In 2002, FDA approved a supplemental NDA under Subpart H, allowing the drug to be marketed with a restricted distribution program and substantially more limited indication. For Accutane, which was originally approved for marketing in 1982, FDA approved a supplemental NDA under the restricted distribution provision of Subpart H in 2005 in order to require a more formal restricted distribution program that linked Accutane prescribing and dispensing to pregnancy testing results.



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because the course of pregnancy was well-documented and the effect of the treatment was self-evident. Revlimid, Thalomid, Plenaxis, and Xyrem were also each approved on the basis of data that included at least one key clinical study that lacked a concurrent control.<sup>47</sup> In contrast to the Mifeprex data, FDA concluded that the lack of concurrent controls in these studies was a weakness because data on the course of the disease in a comparable population was not available to be used as a reliable historical control. For example, Thalomid was approved on the basis of clinical trial data from the published literature as well as a series of retrospective case studies for several dozen patients.<sup>48</sup> Additionally, five of the drugs—Actiq, Revlimid, Thalomid, Tracleer, and Xyrem—were approved on the basis of key clinical studies with relatively small sample sizes of several hundred patients or less. Finally, for Actiq, Plenaxis, Thalomid, and Xyrem, FDA identified data collection issues, such as incomplete documentation, in some of the key data sources.

Another common element was that for six of the drugs, including Mifeprex, FDA issued at least one prior action letter before ultimately approving the drug for marketing. FDA issued one approvable letter before ultimately approving Thalomid and Tracleer. Both Mifeprex and Xyrem received two approvable letters. In some cases the types of issues FDA cited—such as insufficient safety or efficacy data, the need for additional information on the restricted distribution system, or chemistry and manufacturing issues—were similar. For all four of these drugs, the adequacy of proposed distribution restrictions was a significant issue. For Xyrem, FDA's initial approvable action was also linked to the sufficiency of the data provided in the application. FDA issued not approvable letters for both Actiq and Plenaxis prior to their eventual approval. In the case of Actiq, FDA cited multiple deficiencies, such as reliance on a key clinical study with flaws and an inadequate plan for risk management. For Plenaxis, FDA initially concluded that the risks of the drug exceeded its

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<sup>47</sup>FDA approved Plenaxis on the basis of one uncontrolled clinical trial in the indicated population—men with advanced symptomatic prostate cancer—and three concurrently-controlled clinical trials in men with less advanced prostate cancer. FDA approved Xyrem on the basis of one uncontrolled key safety trial, and two concurrently-controlled clinical trials.

<sup>48</sup>FDA considers such case studies to be historically controlled. In this case, the reviewing division concluded that the data were not sufficient to demonstrate the safety and efficacy of Thalomid. However, that decision was overridden by both the Director of the relevant FDA office and the Director of FDA's Center for Drug Evaluation and Research, based on their individual analyses of the available data.

benefits because of the potential for severe, systemic allergic reactions in patients.

As a result of these complexities, the approval process for the Subpart H restricted drugs was typically longer than the process for other drugs. Across the seven drugs with NDAs approved under Subpart H, an average of almost 25 months elapsed from the time that the sponsor submitted its NDA to the time FDA approved the NDA. The length of time to approval ranged from almost 9 months for Revlimid to more than 54 months for Mifeprex. In comparison, in analyses conducted for our 2006 report on new drug development, we found that it took FDA on average almost 18 months to approve NDAs submitted from 1996 through 2002.<sup>49</sup>

We also found that the types of distribution restrictions FDA imposed on Mifeprex were similar to those imposed on the other Subpart H restricted drugs, though the specifics of the restrictions depended on FDA's safe use concern for the drug.<sup>50</sup> (See table 2.) For all of the drugs except Actiq, FDA required some form of program enrollment or registration process. For example, for Mifeprex and three other drugs, FDA required that patients sign written agreements and that physicians enroll in a prescribing program and attest to their qualifications. For five of the drugs, FDA required formal registries of all prescribing physicians and patients.<sup>51</sup> Additionally, for seven of the drugs, FDA required that distribution be limited to authorized distributors or pharmacies.<sup>52</sup> And for eight of the

<sup>49</sup>See, GAO, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49. (Washington, D.C.: Nov. 17, 2006). In contrast, the drugs approved under the surrogate endpoint provision of Subpart H have generally been approved more rapidly than drugs approved under the restricted distribution provision of Subpart H and than drugs approved outside of Subpart H.

<sup>50</sup>Additionally, except for Plenaxis, FDA convened a meeting of the relevant advisory committee prior to each drug's approval under Subpart H to obtain expert input regarding the appropriate actions to address the agency's safe use concerns, including the distribution restrictions that should be required. The advisory committee meetings that FDA has held for the drugs Accutane and Lotronex occurred after each drug was first marketed in the United States, but prior to their approvals under Subpart H.

<sup>51</sup>FDA has used various types of registries as a mechanism to collect data on patients, providers, and others as a tool for monitoring outcomes of interest.

<sup>52</sup>Two of the drugs—Actiq and Xyrem—were approved as controlled substances and therefore subject to the restrictions imposed by the Controlled Substances Act. Requirements imposed under this act are enforced by the Drug Enforcement Administration and are distinct from the distribution restrictions imposed on these drugs by FDA under Subpart H. See, e.g., 21 U.S.C. § 822; 21 C.F.R. § 1301.11 (2007).



drugs, FDA required that the sponsor establish a process to ensure that dispensing or distribution of the drug was contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. FDA also required that all of the sponsors implement some form of educational program for patients, prescribers, or pharmacists, though FDA did not require that prescribing physicians participate in formal training for any of the drugs. For six of the nine drugs, FDA required that the sponsor report periodically to the agency specifically on implementation of their restricted distribution programs. For seven of the drugs, FDA required that sponsors report to the agency on specific adverse events—such as fetal exposures or liver toxicity—more frequently than is required for other drugs. In the case of Mifeprex and Xyrem, at the time the drugs were approved, FDA did not require that the sponsors submit additional adverse event reports beyond those required for all approved drugs, but did require that physicians agree to report specific types of adverse events to the sponsor.

**Table 2: Selected Features of Restricted Distribution Programs Imposed by FDA at Time of Approval under Subpart H**

Features Required at Approval	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
Program enrollment or registration <sup>a</sup>	✓	✓		✓	✓	✓	✓	✓	✓
Limited distribution channels <sup>b</sup>	✓			✓	✓	✓	✓	✓	✓
Dispensing or distribution contingent on verification <sup>c</sup>	✓	✓		✓	✓	✓	✓	✓	✓
Sponsor developed educational programs <sup>d</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reporting specific to implementation of restricted distribution program		✓	✓	✓	✓		✓		✓
Additional adverse event reporting by the sponsor <sup>e</sup>		✓	✓	✓	✓		✓	✓	✓

Source: GAO analysis of FDA data.

<sup>a</sup>Program enrollment or registration requirements varied across the drugs. For Accutane, Lotronex, Mifeprex, and Plenaxis, FDA required that physicians enroll in a prescribing program and attest to their qualifications. For Accutane, Revlimid, Thalomid, Tracleer, and Xyrem, FDA required formal registries of all prescribing physicians and patients. FDA also required registration of pharmacies, wholesalers, or distributors for Thalomid, Revlimid, and Accutane.

<sup>b</sup>The specific limitations imposed on distribution channels varied across the drugs, and in some cases more than one limitation was required. These limitations included, for example, requiring that a drug only be distributed directly to prescribing physicians, allowing only authorized distributors or wholesalers to ship a drug, and allowing only registered or centralized pharmacies to dispense a drug.

<sup>c</sup>The verification mechanisms varied across the drugs. For example, for Mifeprex, an authorized distributor must verify that a physician has a signed prescriber agreement on file before distributing the drug. For Lotronex, before dispensing and drug, pharmacists must verify that prescriptions include a sticker that is only available to physicians enrolled in the prescribing program. For Accutane, Revlimid, and Thalomid, a registered pharmacy is required to confirm prescription authorizations and that patients have complied with requirements to use one or more methods of contraception before dispensing the drug.

<sup>d</sup>In general, sponsors were required to develop educational materials (such as patient information videos) for patients, and make educational materials and training programs readily available to prescribing physicians, pharmacists, and other groups involved in the restricted distribution program. For some of the drugs, dispensing pharmacists were required to participate in formal training. At the time of Subpart H approval, FDA required medication guides for all of the drugs except Actiq, Plenaxis, and Thalomid.

<sup>e</sup>Sponsors for seven of the drugs were required to submit 15-day alert reports on specific adverse events. Sponsors of four of the drugs were required to provide updates more frequently than typically required for events related to FDA's safe use concern for the drug. For Mifeprex, as part of their prescriber agreement, physicians agreed to report ongoing pregnancies, hospitalizations, transfusions, and other serious events to the sponsor. For Xyrem, FDA required that physicians agree to collect and report to the sponsor information on specific adverse events and inappropriate use of the drug.

Finally, eight of the nine Subpart H restricted drugs were approved with two or more postmarketing study commitments.<sup>53</sup> Each of these had at least one commitment that involved developing a postmarket study to monitor adverse events or patient outcomes of interest for that drug. The number of study commitments FDA required ranged from 2 to 10, depending on the drug. Additionally, for most of the drugs, including Mifeprex, the study protocols for the various commitments had not been finalized at the time of approval.

<sup>53</sup>FDA's approval of Accutane under Subpart H through a supplemental NDA did not include any postmarket study commitments.

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## FDA's Postmarket Oversight of Mifeprux Has Been Consistent with the Agency's Oversight of the Other Subpart H Restricted Drugs

The actions FDA has taken to oversee Mifeprux have been consistent with the actions it has taken to oversee the other Subpart H restricted drugs. FDA has relied primarily on information submitted by the sponsors of all the Subpart H restricted drugs and inspections for three of the drugs to oversee compliance with restricted distribution requirements. FDA has also relied on updates submitted by these sponsors to oversee compliance with postmarketing study commitments and has found that most have unfulfilled commitments. To oversee compliance with adverse event reporting requirements, FDA has reviewed a variety of safety information including reports submitted by the sponsors of all nine of the drugs restricted under Subpart H and has conducted inspections to evaluate compliance with reporting of adverse events for eight of the drugs. As a result, for most of the drugs, FDA has identified deficiencies in compliance with adverse event reporting requirements. To oversee reported adverse events FDA has used similar methods—such as monitoring, investigating, and addressing safety concerns—for Mifeprux and the other eight Subpart H restricted drugs. As a result of its oversight of safety data, FDA has identified postmarket safety concerns for most of the drugs and has used a variety of methods to communicate safety information to health care providers and the public. (See table 3 for an overview of FDA's postmarket oversight of these drugs.)

**Table 3: Selected Features of FDA’s Oversight of Postmarket Safety for Drugs Approved under Subpart H, as of May 2008**

Oversight Activities and Findings	Mifeprex (mifepristone)	Lotronex (alosetron hydrochloride)	Actiq (oral transmucosal fentanyl citrate)	Thalomid (thalidomide)	Tracleer (bosentan)	Xyrem (sodium oxybate)	Plenaxis (abarelix for injectable suspension)	Revlimid (lenalidomide)	Accutane (isotretinoin)
FDA has completed inspection(s) to oversee compliance with distribution restriction requirements <sup>a</sup>	✓				✓	✓			
FDA has classified at least one postmarketing study commitment as unfulfilled <sup>b</sup>	✓	✓	✓	✓	✓		✓	✓	n/a
FDA has conducted inspection(s) to oversee compliance with adverse event reporting requirements <sup>c</sup>	✓	✓	✓	✓	✓	✓	✓		✓
FDA has identified a postmarket safety concern leading to communication of new safety information to public or health care providers <sup>d</sup>	✓	✓	✓	✓	✓	✓		✓	✓

Source: GAO analysis of FDA data.

Note: FDA provided or confirmed data on these selected features of oversight through May 2008.

<sup>a</sup>In May 2008, FDA officials told us that they had conducted such inspections for three additional drugs. However, the reports from those inspections were not yet available. Inspections were in addition to report review.

<sup>b</sup>FDA classifies unfulfilled postmarketing study commitments as ongoing, pending, delayed, released, or terminated; FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarketing study commitments and has submitted the final report for the third and final commitment.

<sup>c</sup>Inspections were in addition to report review conducted for all of the drugs. In the case of Revlimid, FDA inspected Celgene—the sponsor of both Revlimid and Thalomid—before Revlimid was approved in December 2005.

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<sup>d</sup>Communication of new safety information includes activities such as changing product labeling, issuing Public Health Advisories and Safety Alerts, and distributing letters to health care providers.

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## To Oversee Compliance with Distribution Restrictions, FDA Relied on Information Submitted by All Drug Sponsors and Its Own Inspections for Some of the Drugs, Including Mifeprex

For all nine of the drugs that have been approved under the restricted distribution provision of Subpart H, FDA has relied mainly on information submitted by sponsors in required reports to oversee the sponsors' compliance with distribution restrictions. For six of the drugs—not including Mifeprex—FDA relied on reports specific to the drugs' restricted distribution programs.<sup>54</sup> The type of information provided by the sponsors in these documents included data on the operation of the restricted distribution program, such as requirements for distributors, pharmacies, prescribers, and patients participating in the program. In addition, to oversee compliance with the restricted distribution programs for most of the drugs—including Mifeprex—FDA has relied on annual reports, supplemental applications, or periodic reports for required updates on the postmarket use of the drugs, including summaries of updates to the restricted distribution program.<sup>55</sup>

Through the end of 2007, FDA had conducted inspections specifically to oversee sponsors' compliance with distribution restrictions for three of the drugs—Mifeprex, Tracleer, and Xyrem. In the case of Mifeprex, in 2002 FDA conducted routine inspections of two of the drug's distributors to oversee their compliance with distribution restrictions. FDA inspectors reviewed standard operating procedures and other information in order to oversee adherence to the requirements of the restricted distribution program such as procedures for maintaining signed provider agreements, distributing medication guides with shipments of the drug, and maintaining the physical security of the drug. For one of the inspections of Mifeprex distributors, FDA did not issue a citation. For the other inspection, FDA issued a citation in which the agency cited four

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<sup>54</sup>FDA approved six of the nine Subpart H restricted drugs with a requirement that the sponsor report periodically to FDA specifically on implementation of the respective restricted distribution program. Under FDAAA, sponsors of all drugs with an approved REMS will be required to submit periodically to FDA an assessment of their REMS. Pub. L. No. 110-85, § 901(b), 823 Stat. 929, 932, *codified at* 21 U.S.C. § 355-1.

<sup>55</sup>Though FDA's Subpart H regulations provide an expedited process for withdrawing marketing approval for a drug if FDA determines that promotional materials are false or misleading, the agency has not done so for a Subpart H drug. See 21 C.F.R. § 314.530(a)(5) (2007). However, it has issued warning letters citing the sponsors for two of the drugs—Thalomid and Tracleer—for promoting unapproved use of the drug in violation of FDA regulations.

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inconsistencies between the approved distribution plan and the distributor's standard operating procedures. For example, FDA cited the distributor for the absence of certain written procedures pertaining to the distribution of the drug. The sponsor responded to this citation, noting that at the time of approval the distribution plan did not require that distributors prepare such written procedures. Other examples of the inconsistencies FDA noted were serial numbers that had not been properly recorded on a shipping label as required for tracking purposes and the requirement that a medication guide be provided with each dose of the drug was not reflected in the written procedures for processing orders. As a result of its 2006 inspection of the Tracleer restricted distribution program, FDA did not issue a formal citation, but provided recommendations to the sponsor. In its 2007 inspection of the Xyrem restricted distribution program, FDA did not identify any specific deficiencies.<sup>56</sup> However, many of the responsibilities for the program are contracted out to a pharmacy, which was not inspected. The inspection report notes that, for that reason, FDA could not verify whether the sponsor had fulfilled the requirements for the drug's restricted distribution program.

Although FDA's inspections for Mifeprex and Tracleer led to recommendations for improving the respective restricted distribution programs, through the end of 2007, FDA had not conducted inspections of compliance with restricted distribution requirements for six Subpart H restricted drugs. FDA officials told us that the agency has conducted

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<sup>56</sup>FDA's inspection report notes that the sponsor refused to provide FDA access to full reports from audits that the sponsor had conducted to evaluate its contractors' compliance with agreed upon responsibilities under the restricted distribution program.

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inspections of compliance with distribution restrictions for three additional drugs since the beginning of 2008.<sup>57, 58</sup>

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## To Oversee Compliance with Postmarketing Study Commitments, FDA Relied on Sponsors' Data That Found That Most Have Unfulfilled Commitments

For the eight Subpart H restricted drugs approved with postmarketing study commitments, FDA has relied on sponsors' annual reports for updates on the status of each commitment. FDA's reviews of these reports are the basis for its determination of the status of each commitment as fulfilled, submitted, pending, ongoing, delayed, released, or terminated. FDA officials told us that the status of postmarketing study commitments for Subpart H drugs is monitored the same way as those commitments for other drugs.

Seven of the eight Subpart H restricted drugs approved with postmarketing study commitments had at least one commitment that was not fulfilled as of September 2007.<sup>59</sup> Of these seven drugs, most have study commitments that FDA has classified as ongoing, pending, or delayed.<sup>60</sup> In the case of Mifeprex, FDA had categorized both of the drug's postmarketing study commitments—to which the sponsor agreed at time of the drug's approval in 2000—as ongoing until December 2007 when the agency changed the status of one of the commitments to released. For the first commitment—a study to compare outcomes for patients whose

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<sup>57</sup>In 2008, FDA conducted initial inspections specific to the restricted distribution programs for Accutane, Actiq, and Revlimid. In addition, FDA conducted a second such inspection for the Tracleer program. As of May 13, 2008, the results from these inspections were not available.

<sup>58</sup>In February 2007, agency officials told us that they were working to establish a process to conduct regular inspections to oversee sponsors' compliance with distribution restrictions for Subpart H restricted drugs. Since that time, agency officials told us that FDA had decided to combine the inspection of restricted distribution programs with inspections examining compliance with adverse event reporting requirements. However, agency officials noted in May 2008 that FDA is reevaluating its process for conducting inspections in light of recent legislative changes. Under FDAAA, FDA is required to evaluate, at least annually, for one or more drugs that have elements to assure safe use as part of their REMS, whether those elements assure the safe use of the drug, are not unduly burdensome on patient access, and to the extent practicable minimize the burden on the health care delivery system. 21 U.S.C. § 355-1(f)(5)(B).

<sup>59</sup>FDA has documented that the sponsor for Xyrem has fulfilled two of its postmarket study commitments and has submitted the final report for the third and final commitment.

<sup>60</sup>In its June 2006 report on FDA's management of postmarket studies, the Department of Health and Human Services Office of the Inspector General found that it is common across all drugs approved by FDA with postmarket study commitments for sponsors to have unfulfilled commitments.

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health care providers perform a surgical abortion with outcomes for patients who are referred to another facility for follow-up care in the event of treatment failure—the sponsor has reported difficulty in enrolling participants into the study. FDA told us that according to the sponsor, the “vast majority of prescribers” can provide surgical abortion services on site. FDA has opted not to terminate the study, and has categorized it as ongoing. FDA officials told us that this gives the agency additional flexibility in the event that provider or practice patterns change over time, making enrollment of study participants more feasible. The sponsor also has reported enrollment challenges in the case of the second study commitment for Mifeprex—to conduct surveillance of ongoing pregnancies following failure of treatment. FDA officials told us that postmarket experience with the drug has shown that most patients opt to have a surgical abortion in the event that the Mifeprex regimen is not successful in terminating the pregnancy. In December 2007, FDA released the sponsor from this commitment because it determined that the study will no longer provide helpful information because of low enrollment.

FDA has worked with some of the sponsors of the Subpart H restricted drugs to make adjustments to agreed upon commitments that have not been completed.<sup>61</sup> FDA officials told us that the agency has in some cases made changes to a sponsor’s postmarketing study commitments or requested new commitments in addition to those specified at approval. For example, FDA recommended several additional postmarketing study commitments for Thalomid following the agency’s approval of an expanded indication for the drug. In the case of Tracleer, FDA recommended changes to some of the drug’s study commitments. FDA had not requested additions or changes to the postmarketing study commitments for Mifeprex until the agency released the sponsor from its commitment to conduct surveillance of ongoing pregnancies following failure of treatment.

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<sup>61</sup>FDA may withdraw approval of a drug approved under Subpart H if a sponsor does not carry out its required postmarketing studies with due diligence. 21 C.F.R. § 314.530(a)(2) (2007). According to FDA, the regulations only require postmarketing study commitments for drugs approved under the surrogate endpoint provision (21 C.F.R. § 314.510) and not for drugs approved under the restricted distribution provision (21 C.F.R. § 314.520). FDAAA provides FDA with additional authority with regard to requiring postmarketing studies and/or trials. See 21 U.S.C. § 355(o)(3).



## To Oversee Compliance with Adverse Event Reporting Requirements, FDA Reviewed Sponsors' Data, Conducted Inspections and Identified Deficiencies for Most of the Drugs

To oversee compliance with adverse event reporting requirements, FDA has both reviewed data submitted by sponsors in required reports and conducted inspections. Sponsor reporting for the drugs has included annual reports in which the sponsor provided a summary of the adverse events reported in the previous year; periodic update reports which inform FDA of adverse events monthly, quarterly, or at some other interval established by FDA; and 15-day alert reports for events that are both serious and unexpected. In addition, in some cases sponsors have agreed or FDA has required them to provide 15-day alert reports for other types of serious adverse events. For example, the sponsor of Mifeprex agreed to provide 15-day alert reports for cases of serious infection and ruptured ectopic pregnancy in women who used the drug, and FDA required the sponsor of Thalomid to report suspected or confirmed pregnancy in women taking that drug.<sup>62</sup> In some cases, including for Mifeprex, FDA specifically documented its assessments of adverse event reporting contained in annual, periodic update, or 15-day alert reports or reports submitted to the AERS database. FDA officials told us that staff review all submitted reports, but do not always document their reviews.

In addition to relying on reports submitted by the sponsors, FDA has conducted inspections specifically to oversee the sponsors' compliance with adverse event reporting requirements for eight of the nine drugs, including Mifeprex.<sup>63</sup> Between 2001 and May 2008, FDA had conducted 19 such inspections with a range of none to four inspections conducted for each drug.<sup>64</sup> In the case of Mifeprex, FDA has conducted three inspections—in 2002, 2004, and 2006—related to adverse event reporting. In these inspections, FDA reviewed a variety of documents pertaining to adverse event reporting for Mifeprex, including standard operating procedures, product labeling, MedWatch reporting forms, 15-day alert

<sup>62</sup> Mifeprex labeling specifically cautions against the use of the drug in women with ectopic pregnancy. The sponsor has noted that the condition is not an adverse drug experience as FDA defines the term.

<sup>63</sup> As of May 2008 FDA had not conducted an adverse event reporting inspection for the sponsor of Revlimid since this drug was approved under Subpart H. The agency inspected Celgene—the sponsor of Revlimid and Thalomid—in 2001, 2002, 2004, and 2005, but these inspections occurred before Revlimid was approved in December 2005. FDA officials told us they did not have specific goals for how frequently sponsors are inspected to monitor compliance with adverse event reporting requirements.

<sup>64</sup> These inspections include two inspections of the sponsor of Accutane (isotretinoin). FDA conducted an additional four adverse event reporting inspections of sponsors or the manufacturer of generic isotretinoin products.

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reports, complaint file, periodic update reports on adverse events, and annual NDA reports. In addition, FDA documented reviews of samples of the sponsor's adverse event reports for completeness, accuracy, and timeliness.

As a result of the Mifeprex inspections, FDA issued citations for deficiencies related to the accuracy, completeness, or timeliness of some reports as well as for the sponsor's failure to follow certain procedures for handling some adverse event follow-up activities. In each of the Mifeprex inspections, FDA identified some examples of misclassified reports—events which FDA said should have been submitted as 15-day alert reports rather than in periodic reports. For example, FDA cited the sponsor for not classifying some events resulting in hospitalization as serious events and thus not reporting those events as 15-day alert reports. In another inspection, FDA found that some of the sponsor's procedures for reporting and following up on adverse events were inadequate or had not been developed. These deficiencies were similar to those FDA found for other drugs, and FDA identified fewer problematic reports for Mifeprex than for some of the other Subpart H restricted drugs. Following each of the inspections for Mifeprex, the sponsor provided a written response to FDA in which it either agreed to address FDA's findings or noted its disagreement with the deficiencies FDA cited. For example, following the first inspection, the sponsor agreed to address the examples of misclassified or incomplete reporting FDA cited and to reinforce procedures for handling adverse event-related correspondence with its staff. In some cases the sponsor disagreed with FDA's characterization of a deficiency or presented evidence to refute a claim that it had not complied with a reporting requirement or procedure.

As a result of FDA's inspections for the other seven drugs, the agency issued written citations to six of the sponsors for deficiencies. In addition, FDA noted only "oral observations" for the other sponsor. Similar to the Mifeprex inspections, FDA staff reviewed information such as sponsor documentation and standard operating procedures related to adverse event reporting for the other seven drugs for which it conducted inspections. As it did for the Mifeprex inspections, FDA reviewed samples of adverse event reports for completeness, accuracy, or timeliness for most of the other drugs. As it did with Mifeprex, FDA cited some sponsors for deficiencies such as incomplete or late reporting of adverse events or failure to adhere to certain procedures for reporting. For example, FDA cited the sponsor of Thalomid for failure to submit several reports of serious and unexpected adverse events as a 15-day alert report and for late reporting of some other adverse events that included deaths and

hospitalizations. In addition, FDA issued an untitled letter to the sponsor citing its failure to review and submit 82 reports of serious and unexpected adverse events within the required time frame.

FDA was not always consistent in how it documented deficiencies in adverse event reporting. In some of its inspections FDA documented the same type of deficiency as a citation while in others it noted them as oral observations or discussion points. For example, FDA did not issue a citation for the sponsor of Tracleer after inspectors noted 52 late 15-day reports—instead discussing the late reports with the sponsor at the close of the inspection. However, in its first inspection of the sponsor for Mifeprex, FDA issued a citation for failure to file a single 15-day report within the required 15 days. FDA also cited the sponsor for 6 late 15-day reports in each of its two subsequent inspections, although the sponsor refuted this finding in written responses following each inspection. As in the case of Mifeprex, sponsors responded to FDA in writing to describe actions they had taken to address deficiencies or to disagree with FDA’s conclusions following an inspection.

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### To Oversee Postmarket Safety, FDA Used Similar Methods to Review Reported Adverse Events and Took a Variety of Actions in Response to Emerging Concerns

FDA has used similar methods to oversee postmarket safety—monitoring, investigating, and taking action on emerging safety concerns—for Mifeprex and the other eight Subpart H restricted drugs. For Mifeprex, FDA has routinely reviewed the available information on reported adverse events from sources such as annual reports, periodic update reports, 15-day alerts, and data from its AERS database. Since the time Mifeprex was approved, FDA has documented regular reviews and summarized the available data on adverse event reports to monitor the drug’s safety. FDA believes that, because the distribution system for Mifeprex requires that prescribing physicians agree to report hospitalizations and other serious adverse events, it is unlikely there are significant numbers of these events that are not reported to FDA. However, FDA acknowledges that because the reporting system is voluntary, the agency cannot be certain that they have reports of all serious adverse events.

FDA officials have concluded that, with the exception of the cases of fatal infection, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected based upon the medical literature on adverse events following medical abortion. In its May 2006

response to congressional inquiries regarding Mifeprex,<sup>65</sup> FDA stated that the most commonly reported serious adverse events had been blood loss requiring a transfusion, infection, and ectopic pregnancy. FDA estimated that 0.023 percent of U.S. women who had taken Mifeprex have required transfusion, compared to a transfusion rate of 0.15 percent observed in international studies of the drug. FDA also noted that the rate of ectopic pregnancy among U.S. women who had used Mifeprex was 0.005 percent, compared to the overall rate of 1.3 to 2 percent in all U.S. pregnancies. Based on the medical literature, FDA estimated that fewer than 1 percent of patients will develop an infection of any kind following medical abortion with Mifeprex.

According to FDA, as of May 2008, among the estimated 915,000 U.S. women who had taken Mifeprex for termination of pregnancy since its approval, the agency was aware of seven deaths that may be related to the use of the drug.<sup>66</sup> Six of the deaths were due to severe infection, and one death involved an undiagnosed ectopic pregnancy. Of the cases involving infection, five of the women were infected with a rare bacterium, *Clostridium sordellii*, while one woman was infected with the bacterium *Clostridium perfringens*. With assistance from the Centers for Disease Control and Prevention (CDC) and other outside experts, FDA has investigated all reported infection-related deaths in U.S. women who have taken the Mifeprex regimen for termination of pregnancy. These investigations included requesting the medical records and autopsy reports for each case; evaluating available adverse event data from the United States, the United Kingdom, and the World Health Organization; consulting with scientific experts and health care providers from inside and outside FDA; and microbiological testing to identify the bacterium involved. In addition, FDA evaluated samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths to test for contamination with the bacteria.<sup>67</sup> FDA found that in the six cases of death

<sup>65</sup>FDA statement to the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, May 17, 2006.

<sup>66</sup>In her testimony to Congress on May 17, 2006, Dr. Janet Woodcock stated FDA was aware of five infection-related deaths in U.S. women. In the course of GAO's research for this study, FDA reported that an additional infection-related death occurred in 2007. In her testimony, Dr. Woodcock also discussed three other cases of deaths in U.S. women who had taken Mifeprex that, following investigation, were determined unlikely to be related to the use of the drug. In addition, she discussed three women in other countries whose deaths were related to the use of mifepristone and misoprostol for medical abortion.

<sup>67</sup>The product tracking provision of the restricted distribution program for Mifeprex enabled FDA to locate the lot numbers for the drugs administered in each of the cases.

due to infection, the women used a regimen of Mifeprex and misoprostol that has not been approved by FDA.<sup>68</sup> FDA has stated that it is aware that many health care providers use modified regimens, and while some of the regimens have been described in the medical literature, FDA has not evaluated the safety and effectiveness of any other regimen than the one described in the drug's approved labeling.

To further explore the nature of the infections, FDA initiated an interagency scientific workshop in May 2006 with CDC and the National Institutes of Health entitled "Emerging Clostridial Disease." These agencies had observed a general increase in the United States in reports of serious clostridial infections including infections in women who had used Mifeprex, that raised questions about *Clostridium's* relationship to fatal illness and pregnancy. According to the meeting minutes, participants discussed recent cases of clostridial infection—including those occurring among women who had taken Mifeprex and misoprostol for termination of pregnancy and those who had not—reviewed what was currently known about these infections, and discussed how to conduct surveillance to ensure that cases and trends of clostridial infections are monitored. At the workshop, a CDC official reported on the history of clostridial infections, including a cluster of ten fatal cases reported in the literature between 1977 and 2001 among previously healthy women. Of the ten cases, eight of the women became infected following childbirth, one became infected following a medical abortion, and the other case was unrelated to pregnancy.

As a result of its investigative efforts, FDA has concluded that the evidence does not indicate that Mifeprex caused the fatal infections. In response to congressional inquiry, FDA stated that "the nature of the relationship between taking a single dose of the drug and the reported cases of serious infection with a rare bacterium is highly uncertain."<sup>69</sup> Laboratory testing of samples from the drug lots of Mifeprex and misoprostol associated with some of the deaths due to infection has

<sup>68</sup>In the case of five of the deaths in the U.S. due to infection, the women used an oral dose of Mifeprex, followed by a dose of misoprostol taken intravaginally. In the other case of death due to infection, the woman used an oral dose of Mifeprex followed by a dose of misoprostol taken by inserting it in the pouch of the cheek. The regimen approved by FDA calls for swallowing doses of both Mifeprex and misoprostol.

<sup>69</sup>See FDA letter to Representative Mark E. Souder, then-Chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, Committee on Government Reform, U.S. House of Representatives, July 31, 2006.

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shown no evidence of contamination with the bacteria.<sup>70</sup> FDA officials have said that the relationship between the infections and the use of unapproved regimens of Mifeprex and misoprostol remains unknown. Some research has suggested that the use of Mifeprex may suppress the immune system which could lead to infection. However, FDA has noted that if this were the case, the agency would expect to see a higher rate of other types of serious infections in patients who had used the drug, which has not been the case. FDA has noted that findings by the CDC and in the medical literature suggest that pregnancy itself—rather than the medication—may be the critical risk factor for women who have become infected with *Clostridium sordellii*.

FDA, working with the drug's sponsor, has taken a variety of steps—such as issuing warnings and making changes to the product labeling—to address safety concerns for Mifeprex that were identified through postmarket monitoring and investigation. For example, in response to reports of ruptured ectopic pregnancy, FDA developed a questions and answers document about the condition and worked with the drug's sponsor to alert health care providers and to highlight the importance of careful screening for the condition. In addition, FDA approved a labeling change to provide information about the importance of evaluating patients for ectopic pregnancy. In response to concerns about serious infections and associated deaths—all of which involved an off-label use of the drug—FDA issued Public Health Advisories to notify healthcare providers about patient deaths and the treatment regimens used in those cases, and to remind them of the regimen FDA has approved, and that FDA has not established the safety of alternative regimens. In addition, FDA issued a news release, reviewed letters from the sponsor to health care providers and emergency room directors to alert them to the safety concerns regarding serious infection, and approved changes to product labeling including revisions to the warning to include information about the deaths due to serious infection.<sup>71</sup> FDA also has established a Web site with information about Mifeprex, questions and answers about the drug, and

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<sup>70</sup>FDA officials told us that the agency did not test for bacterial contamination of the specific lot associated with the most recent death because examination of the prior lots revealed no contamination.

<sup>71</sup>FDA officials told us that the sponsor distributed a letter to all health care providers who had signed the prescriber's agreement as of the time of the distribution of the letter and distributed a letter to all emergency room directors in the United States.



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links to other safety-related information.<sup>72</sup> FDA used labeling changes—including updating the medication guide that prescribers agree to discuss with their patients—and information posted on its Web site to remind consumers and health care providers that FDA has not assessed the safety and efficacy of any regimen other than the one approved for the drug and indicated in its labeling.

FDA has similarly monitored adverse events for the other Subpart H restricted drugs. As FDA has done with Mifeprex, the agency has documented periodic safety reviews of the available information it had on reported adverse events for all of the other drugs. FDA's reviews analyzed data on reported adverse events from sources such as annual NDA reporting, periodic update reports, 15-day alerts, and data from the AERS database. Some FDA reviews summarized the available data on a specific type of adverse event—like liver toxicity, or severe bleeding—or adverse events in general, in order to determine whether the data suggest an emerging safety concern for the drug. In addition, in some cases, as it did with Mifeprex, FDA has sought the advice and assistance of other federal agencies and outside experts to investigate serious adverse events.

As a result of its monitoring activities, FDA has identified postmarket safety concerns for most of the Subpart H restricted drugs and has taken similar actions to address them. When FDA has found safety concerns related to a Subpart H restricted drug, it has worked with the drug's sponsor to employ a variety of measures to ensure the drug's safe use. These have included adding or strengthening a warning on the label, issuing a Public Health Advisory, and sending letters to health care providers to alert them to a safety risk. FDA has approved safety-related labeling changes, such as boxed warnings, for eight of the nine drugs. In the case of four of the drugs, including Mifeprex, the agency issued a Public Health Advisory or Safety Alert. The sponsors of five of the drugs including Mifeprex sent a letter to health care providers who prescribe (or may prescribe) the drug to alert them of safety concerns or to communicate new information regarding the drug. For example, in the case of Tracleer, adverse event reports revealed an increased risk of liver damage in patients who were treated with the drug. As a result, FDA and the sponsor notified health care providers of the risk by issuing a Safety Alert, highlighting the need for continued monitoring of liver function in

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<sup>72</sup>FDA's Web site for Mifeprex safety information is located at: <http://www.fda.gov/cder/drug/infopage/mifepristone/default.htm>



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patients using the drug. The sponsor added a boxed warning about potential liver injury to the labeling and issued a letter to health care providers to alert them to the potential risk. In general, the actions FDA took in response to safety concerns were similar across all of the drugs.

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## Agency Comments

We provided HHS with a draft of this report for review. HHS informed us that it did not have general comments on the draft report. In addition, HHS provided technical comments, which we incorporated as appropriate.

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As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Marcia Crosse  
Director, Health Care

# Appendix I: Select Drugs Approved by FDA with Restricted Distribution

Drugs approved under the restricted distribution provision of Subpart H	Condition treated	Application type (year first approved under Subpart H)
Accutane (isotretinoin)	Severe recalcitrant nodular acne.	Supplemental NDA (2005)
Actiq (oral transmucosal fentanyl citrate)	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.	NDA (1998)
Lotronex (alosetron hydrochloride)	Severe diarrhea predominant irritable bowel syndrome (IBS) in women who have: chronic IBS symptoms (generally lasting 6 months or longer), had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and failed to respond to conventional therapy.	Supplemental NDA (2002)
Mifeprex (mifepristone)	Medical termination of intrauterine pregnancy through 49 days' pregnancy.	NDA (2000)
Plenaxis (abarelix for injectable suspension)	Palliative treatment of men with advanced symptomatic prostate cancer, with specified risks or symptoms.	NDA (2003)
Revlimid (lenalidomide)	Treatment of a limited subset of patients with transfusion dependent anemia.	NDA (2005)
	Treatment of multiple myeloma patients who have received at least one prior therapy.	Supplemental NDA
Thalomid (thalidomide)	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.	NDA (1998)
	Newly diagnosed multiple myeloma.	Two Supplemental NDAs <sup>a</sup>
Tracleer (bosentan)	Pulmonary arterial hypertension.	NDA (2001)
Xyrem (sodium oxybate)	Cataplexy associated with narcolepsy.	NDA (2002)
Select Drugs with restricted distribution imposed outside of Subpart H		Application type (year first approved)
Clozaril (clozapine)	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.	NDA (1989)
Tikosyn (dofetilide)	Irregular heartbeats (atrial fibrillation and atrial flutter).	NDA (1999)
Trovan (trovafloxacin/alatrofloxacin)	Serious, life- or limb-threatening infections in an inpatient healthcare setting.	n/a <sup>b</sup> (1997)

Source: GAO analysis of FDA data.

Note: We list each drug by its trade name with its chemical name in parentheses.

<sup>a</sup>These supplemental NDAs were approved under both the restricted distribution and surrogate endpoint provisions of Subpart H.

<sup>b</sup>Trovan was not originally approved with distribution restrictions. Based on postmarket evidence of serious liver injury in some patients, the sponsor agreed to FDA's requests to limit the distribution of Trovan to patients with specific symptoms only in inpatient settings. However, these restrictions were not associated with a supplemental application.

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## Appendix II: Detailed Description of Distribution Restrictions for Mifeprex

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FDA approved Mifeprex with the following specific restrictions on distribution:

- Mifeprex must be provided by or under the supervision of a physician who possesses adequate qualifications and agrees to provide the treatment according to several guidelines. To accomplish this, the system required that prescribing physicians register with an authorized distributor by providing a signed Prescriber's Agreement attesting to the following:
  - Possesses the ability to assess the duration of pregnancy accurately.
  - Possesses the ability to diagnose ectopic pregnancies.
  - Possesses the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
  - Has read and understood the prescribing information about Mifeprex.
  - Will provide each patient with a medication guide and fully explain the procedure to each patient, provide her with a copy of the medication guide and Patient Agreement, give her an opportunity to read and discuss both the medication guide and the Patient Agreement, obtain her signature on the Patient Agreement and sign it as well.
  - Will notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
  - Will report any hospitalization, transfusion or other serious events to the sponsor or its designate.
  - Will record the Mifeprex package serial number in each patient's record.
- Provisions for the physical security of the drug during distribution such as
  - Direct distribution of the drug through select authorized distributors to physicians who have signed the Prescriber's Agreement, which includes providing their medical license number. Distributors are

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**Appendix II: Detailed Description of  
Distribution Restrictions for Mifeprex**

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required to ensure that the physician is registered before distributing the drug.

- Secure manufacturing, receiving, distribution, shipping, and return procedures, including unique serial numbers on packaging and tamper-proof seals.

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## Appendix III: Prescriber's Agreement for Mifeprex Distribution

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The following is the prescriber's agreement at the time of the Mifeprex approval. Under the restricted distribution program for Mifeprex, the agreement is provided—by the sponsor's licensee Danco Laboratories, Inc.—to all providers to be signed and returned before the prescriber can receive any shipments of Mifeprex.

**Appendix III: Prescriber's Agreement for  
Mifeprex Distribution**

**M I F E P R E X™  
(Mifepristone) Tablets, 200 mg  
PRESCRIBER'S AGREEMENT**

We are pleased that you wish to become a provider of Mifeprex® (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, [www.earlyoptionpill.com](http://www.earlyoptionpill.com).

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

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**Appendix III: Prescriber's Agreement for  
Mifeprex Distribution**

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event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC  
P.O. Box 4816  
New York, NY 10185  
1-877-4 Early Option (1-877-432-7596)  
[www.earlyoptionpill.com](http://www.earlyoptionpill.com)



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# Appendix IV: GAO Contact and Staff Acknowledgments

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## GAO Contact

Marcia Crosse, (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov).

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## Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Jill Center; Chad Davenport; and Cathy Hamann made key contributions to this report. Julian Klazkin also contributed.

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